

# Study of Cross-Reactivity Between Proton Pump Inhibitors

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## ■ Abstract

Several studies have demonstrated different cross-reactivity patterns between proton pump inhibitors (PPIs). The aim of this study was to investigate cross-reactivity between commercially available PPIs and establish a procedure for performing cutaneous tests for verifying PPI allergy.

We performed skin prick and intradermal tests with all commercially available PPIs in 5 patients with clinical allergy to omeprazole and observed positive results in all patients.

We report 5 cases of immunoglobulin (Ig) E-mediated allergy to omeprazole and document cross-reactivity by skin testing between all the PPIs studied. We also found that the probability of confirming an IgE-mediated mechanism with skin tests decreases with time. Finally, we propose a hypothesis that could explain the different PPI cross-reactivity patterns reported.

**Key words:** Esomeprazole. Lansoprazole. Omeprazole. Pantoprazole. Proton pump inhibitors. Rabeprazole.

## ■ Resumen

Varios estudios demuestran diferentes patrones de reactividad cruzada entre los inhibidores de la bomba de protones. El objetivo es investigar la reactividad cruzada entre todo el grupo y llevar a cabo un procedimiento para realizar pruebas cutáneas que verifiquen la alergia a estos fármacos.

Estudiamos cinco casos de alergia a omeprazol y realizamos pruebas cutáneas en prick e intradermorreacción a cada paciente, con todos los inhibidores de la bomba de protones. Las pruebas cutáneas fueron positivas en todos ellos, con cada uno de los fármacos.

Los cinco casos presentaron alergia IgE mediada a omeprazol y evidencia de reactividad cruzada entre todo el grupo de fármacos inhibidores de la bomba de proteasa detectada mediante pruebas cutáneas.

También hemos observado que la probabilidad de confirmar un mecanismo IgE mediado en prueba cutánea disminuye con el paso del tiempo. Sugerimos una hipótesis que podría explicar los diferentes patrones de reactividad cruzada entre los inhibidores de la bomba de protones.

**Palabras clave:** Esomeprazol. Lansoprazol. Omeprazol. Pantoprazol. Inhibidores de la bomba de protones. Rabeprazol.

## Introduction

Proton pump inhibitors (PPIs) are powerful drugs used to treat peptic ulcer and gastroesophageal disease. They act selectively on the final stage of the process of gastric acid secretion, namely on the H<sup>+</sup>/K<sup>+</sup>-ATPase or proton pump. This enzyme plays an essential role in the process of H<sup>+</sup> secretion and PPIs exert a very specific action on the parietal cell as

they need an environment with very low pH levels, which only exist in this cell.

Omeprazole was the first drug to be developed in the class of PPIs. It was introduced in 1979 but since then other PPIs have emerged, including lansoprazole, pantoprazole, rabeprazole, and esomeprazole.

PPIs have proven to be highly efficacious and safe. They have a very effective therapeutic action; 20 mg of omeprazole

reduces acid production by 90% to 95% in 24 hours, meaning that it is 10 to 100 times more effective than histamine H<sub>2</sub>-receptor antagonists. In patients with demonstrated allergy to PPIs, a desensitization protocol should be considered in cases where the drug is really necessary [1].

While clinical adverse events are uncommon and involve mainly gastrointestinal and central nervous system reactions, PPIs have been reported to cause immunoglobulin (Ig) E hypersensitivity reactions [1-13], non-IgE-mediated immunological reactions such as contact dermatitis [14,15], toxic epidermal necrolysis [16,17], cutaneous leukocytoclastic vasculitis [18], and drug rash with eosinophilia and systemic symptoms syndrome [19].

Numerous studies have investigated cross-reactivity between PPIs [2,3,5,7-9,11,12,13,19].

We present a study of cross-reactions between commercially available PPIs in adult patients allergic to omeprazole studied at our allergy clinic and review other PPI cross-reactivity reports in the literature.

## Case Description

We studied 5 cases of clinical allergy to omeprazole, the details of which are summarized in Table 1.

The first patient, a 59-year-old woman, was treated for stomach ache with intravenous omeprazole 40 mg and within 5 minutes developed an anaphylactic reaction consisting of pruritus and urticaria on her whole body, increased sweating, low blood pressure (90/70), and loss of consciousness. She required treatment with parenteral adrenaline, methylprednisolone, and dexchlorpheniramine.

The second patient, also a 59-year-old woman, developed generalized urticaria 2 hours after ingestion of omeprazole 20 mg as a gastric protector; she was treated with methylprednisolone.

The third patient, a 56-year-old man, presented with sudden onset of pruritic erythema and swelling of the palms

and soles, malaise, dizziness, generalized urticaria, difficulty in swallowing, and dysphonia that developed within 45 minutes of ingestion of omeprazole 40 mg as a gastric protector; he required intravenous methylprednisolone and dexchlorpheniramine.

The fourth patient was a 37-year-old man with a medical history of gastric ulcer and hiatal hernia, occasionally self-medicated with omeprazole. In the previous year he had developed 4 episodes of epigastralgia, palm itch, intense perspiration, generalized cutaneous erythema, and angioedema of the hands. In the last 2 cases he was treated with parenteral adrenaline and intravenous saline to treat a sharp decrease in blood pressure, with a good outcome. After the third episode, he was studied in our allergy clinic but was unable to suggest causes common to all 3 episodes. An allergologic study for anaphylaxis was normal (skin prick tests [SPTs] with a series of common inhalant and food allergens, hemogram, biochemistry, complement, antinuclear antibodies, hepatitis serology, parasite infection, hormonal investigations, abdominal ultrasound, and chest radiograph), so we recommended the patient kept a diary. After the fourth episode, we observed that the patient had taken an omeprazole capsule 30 minutes before the reaction.

The fifth patient, a 30-year-old woman, presented pruritic erythema and swelling of the palms and soles, generalized urticaria, face angioedema, difficulty in breathing, nausea, and vomiting 10 minutes after ingestion of omeprazole 20 mg for epigastralgia. She required parenteral adrenaline, methylprednisolone, and dexchlorpheniramine.

We decided to study cross-reactivity between PPIs in the 5 patients by performing SPTs with omeprazole (vial) 40 mg/mL, pantoprazole (vial) 40 mg/mL, esomeprazole (vial) 40 mg/mL, rabeprazole (tablet) 10 mg/mL, and lansoprazole (tablet) 15 mg/mL. Histamine and saline were used as controls. In patients with negative results, we performed intradermal tests using 1:1000, 1:100, and 1:10 dilutions of the above solutions. In patients with negative results in all cutaneous tests, it was decided to perform oral challenges. All patients provided their informed consent for these tests.

Table 1. Characteristics of Reactions

	Age, y	Symptoms	Latency	Skin Tests
Patient 1	59	Anaphylaxis	5 minutes	Positive to all PPIs
Patient 2	59	Generalized urticaria	2 hours	Positive to all PPIs
Patient 3	56	Anaphylaxis	45 minutes	Positive to all PPIs
Patient 4	37	Anaphylaxis	30 minutes	Positive to all PPIs
Patient 5	30	Anaphylaxis	10 minutes	Positive to all PPIs

Abbreviation: PPIs, proton pump inhibitors.

Table 2. Results of Skin Tests

	Patient 1 Histamine, 8 mm; saline, negative	Patient 2 Histamine 7 mm; saline, negative	Patient 3 Histamine, 8 mm; saline, negative	Patient 4 Histamine, 8 mm; saline, negative	Patient 5 Histamine, 6 mm; saline, negative
<b>Omeprazole</b>					
SPT	Positive, 8 mm	Positive, 8 mm	Positive, 14 mm	Positive, 8 mm	Positive, 7 mm
ID test	NP	NP	NP	NP	NP
0.04 mg/mL					
0.4 mg/mL					
4 mg/mL					
<b>Pantoprazole</b>					
SPT	Positive, 9 mm	Negative	Negative	6 mm wheal	Positive, 7 mm
ID test	NP				NP
0.04 mg/mL		Negative	Negative	Positive, 9 mm	
0.4 mg/mL		Negative	Positive, 9 mm	NP	
4 mg/mL		Positive, 8 mm	NP	NP	
<b>Esomeprazole</b>					
SPT	6 mm wheal	Negative	Negative	Positive, 8 mm	Positive, 8 mm
ID test				NP	NP
0.04 mg/mL	Positive, 9 mm	Negative	Negative		
0.4 mg/mL	NP	Negative	Positive, 10 mm		
4 mg/mL	NP	Positive, 9 mm	NP		
<b>Rabeprazole</b>					
SPT	Negative	Negative	5-mm wheal	Positive, 8 mm	Positive, 6 mm
ID test				NP	NP
0.01 mg/mL	Negative	Negative	Positive, 8 mm		
0.1 mg/mL	Positive, 8 mm	Negative	NP		
1 mg/mL	NP	Positive, 8 mm	NP		
<b>Lansoprazole</b>					
SPT	Negative	Negative	Negative	6-mm wheal	Positive, 6 mm
ID					NP
0.015 mg/mL	Negative	Negative	Negative	Positive, 10 mm	
0.15 mg/mL	Positive, 8 mm	Negative	Positive, 8 mm	NP	
1.5 mg/mL	NP	Positive, 8 mm	NP	NP	

Abbreviations: ID, intradermal; NP, not performed; SPT, skin prick test.

Six months later, patients 1 and 2 agreed to repeat the cutaneous tests with omeprazole at the same dilutions. The results of these tests are shown in Table 2.

In patient 1, the SPTs to omeprazole and pantoprazole were positive. Esomeprazole yielded a positive result but smaller than that produced by histamine. Intradermal tests were positive to rabeprazole, lansoprazole, and esomeprazole. Six months later, the patient had a negative SPT to omeprazole but a positive intradermal test with the 1:100 dilution (0.4 mg/mL).

In patient 2, the SPTs were positive to omeprazole and negative to pantoprazole, lansoprazole, rabeprazole, and esomeprazole. Intradermal tests were positive to

pantoprazole, rabeprazole, lansoprazole, and esomeprazole. Six months later, the patient showed a negative STP to omeprazole and a positive intradermal test with the 1:100 dilution (0.4 mg/mL).

In patient 3, the SPT was positive to omeprazole (14-mm wheal) and the intradermal tests were positive to pantoprazole, rabeprazole, lansoprazole, and esomeprazole.

Patient 4 had positive SPTs to omeprazole, esomeprazole, and rabeprazole. Pantoprazole and lansoprazole also yielded positive reactions but smaller than those produced by histamine. The intradermal tests were clearly positive to lansoprazole and pantoprazole.

Finally, in patient 5, the SPTs were positive to all 5 PPIs analyzed.

For ethical reasons, oral challenge testing was not performed in any of the patients with a positive cutaneous test due to the risk of a systemic reaction [3,8,12].

Fourteen controls were performed with all the extracts and dilutions and all were negative.

## Discussion

The incidence of hypersensitivity reactions to PPIs is increasing due to the growing use of these drugs, which are both highly effective and frequently used without a medical prescription.

The cutaneous tests performed showed an immediate-type allergic reaction to the 5 PPIs tested in all cases. The dilutions used to perform these tests could be used as a reference guide in professional allergy training to test hypersensitivity to PPIs in in vivo diagnosis. The negative control results excluded the possibility of an irritant response. Ranitidine was well-tolerated by all our patients and therefore used as an alternative.

Gamboa et al [4] described the possibility of an in vitro diagnostic test for allergy to omeprazole via a flow-cytometric cellular allergen stimulation test.

Our study, conducted in 2 stages, proved that the probability of confirming an IgE-mediated mechanism via cutaneous tests decreases with time, as occurs with  $\beta$ -lactam

antibiotics [20]. This clearly highlights the importance of studying drug allergy as early as possible to minimize risks related to oral challenges.

On performing a meticulous analysis of the clinical cases reported in the literature, we observed different patterns of cross-reactivity between PPIs.

### Pattern 1

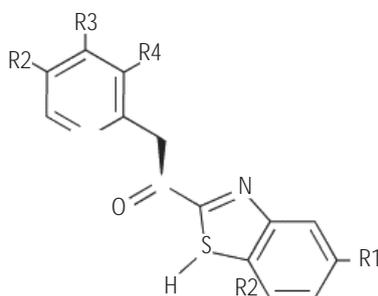
Patients diagnosed with an allergy to a single PPI, (frequently omeprazole) who present cross-reactions with all other PPIs studied [2,3,5,10,13]. We could include our 5 patients in this pattern. Patients that fit this pattern, therefore, are those that experience an immediate reaction to a PPI and have cross-reactivity to all other PPIs.

### Pattern 2

- Patients with allergy to lansoprazole that develop cross-reactivity with rabeprazole [7,8], but tolerate omeprazole, pantoprazole, and esomeprazole.
- Patients with allergy to omeprazole that develop cross-reactivity with pantoprazole, but tolerate lansoprazole [12] (and perhaps rabeprazole).

Patients that fit pattern 2 are those with an allergy to omeprazole-pantoprazole (and perhaps esomeprazole due to its similar chemical structure to omeprazole) and tolerance of lansoprazole-rabeprazole, or vice versa.

These patterns could be explained by the hypothesis



	R1	R2	R3	R4
Omeprazole	-OCH <sub>3</sub>	-CH <sub>3</sub>	-CH <sub>3</sub>	-CH <sub>3</sub>
Lansoprazole	-	-	-OCH <sub>2</sub> -CF <sub>3</sub>	-CH <sub>3</sub>
Pantoprazole	-OCF <sub>2</sub> H	-	-OCH <sub>3</sub>	-OCH <sub>3</sub>
Rabeprazole	-	-	-O(CH <sub>2</sub> ) <sub>3</sub> -OCH <sub>3</sub>	-CH <sub>3</sub>
Esomeprazole	-OCH <sub>3</sub>	-CH <sub>3</sub>	-OCH <sub>3</sub>	-CH <sub>3</sub>

Figure. Proton pump inhibitor (PPI) structure: the common structure of the PPIs is shown in the figure and the different lateral chains in the table.

based on the chemical structure of PPIs proposed by Perez Pimiento [8] and in agreement with Lobera [12] because these drugs are modified benzimidazoles with a pyridine ring, differing by virtue of substitutions on both rings. Omeprazole, esomeprazole, and pantoprazole have changes in their benzimidazole rings, whereas lansoprazole and rabeprazole have changes in their pyridine ring (the structure of these drugs and their lateral chains are shown in the Figure).

### Pattern 3

There is only 1 report of a patient developing immediate allergy to omeprazole and tolerance of pantoprazole and lansoprazole [11]; (rabeprazole and esomeprazole were not studied).

Patients that fit pattern 3 are those with an allergy to a single PPI and tolerance of other PPIs.

We believe that our hypothesis regarding these patterns of cross-reactivity could be confirmed in the future, as more patients with PPI allergy are studied. It is very important to perform studies with all commercial PPIs (omeprazole, pantoprazole, esomeprazole, lansoprazole, and rabeprazole).

The use of a standardized PPI skin test procedure will provide greater knowledge on allergy to these drugs. Until then, it is necessary to perform an allergologic study before offering alternatives to each patient.

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